## REMARKS

Rejection of Claims 16, 20-22, 27-28 and 40 Under 35 U.S.C. § 103(a) (Item 5 of Office Action)

Claims 16, 20-22, 27, 28 and 40 have been rejected under 35 U.S.C. § 103(a) as it is said they are obvious over Stamler *et al.* (WO 93/09806).

Stamler *et al.* (WO 93/09806) disclose S-nitroso-proteins, in particular, S-nitroso-tPA (tPA is tissue plasminogen activator), S-nitroso-BSA, S-nitroso-cathepsin B, S-nitroso-lipoprotein and S-nitroso-immunoglobulin, and methods for producing the same, using NO or $NaNO_2$ as the reagent under acidic conditions. They also report a method which they claim results in the synthesis of S-nitroso-hemoglobin. However, this compound was not produced by any method reported in WO 93/09806, as attested to in the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 mailed to the Patent Office on January 6, 1999. Methods used to synthesize other S-nitroso-proteins, which might have been expected to nitrosate or polynitrosate hemoglobin, dissociated hemoglobin into its subunits, oxidized the heme Fe and rendered the product fragments useless for carrying oxygen. Methods described in the specification that resulted in the synthesis of nitrosated hemoglobins are substantially different from the unsuccessful acidified nitrite method described in WO 93/09806.

The Examiner states that "[t]he Stamler reference teaches methods for "'increasing blood oxygen transport by hemoglobin and myoglobin.'" The WO 93/09806 application states, at page 19, lines 26 and 27, "As demonstrated by the inventors, S-nitrosylation of hemoglobin increases its oxygen-binding capacity." There was no demonstration in WO 93/09806 of any S-nitrosylation of hemoglobin, and no demonstration of any modified form of hemoglobin with increased oxygen binding capacity.

The Examiner further states that "the Stamler reference further teaches that proteins (including hemoglobin), which are nitrosylated on oxygen, carbon or nitrogen sites possess the same therapeutic utility as nitrosylated/nitrated low molecular weight thiol compounds." The WO 93/09806 Stamler reference does not teach any proteins nitrosylated on oxygen, carbon or nitrogen sites, or any therapeutic methods, using such proteins. No person of skill in the art would find any evidence in the Stamler reference that such proteins were made.

Claim 16

As has been explained at length previously, WO 93/09806 does not provide an enabling description of how one of ordinary skill in the art could produce SNO-hemoglobin or hemoglobin that has an NO adduct at a C, N, or O. Nothing in WO 93/09806 provides any evidence that hemoglobin derivatives can be produced with one or more NO adducts at a S, C, N or O atom. The inventors of WO 93/09806 did not set forth any procedure stated as intended to produce hemoglobin with NO adducts at a C, N or O, and did not describe any assay or analytical test to detect such molecules. One of ordinary skill in the art at the time of the invention would be unable to come up with any synthetic procedure to produce hemoglobin derivatives with one or more NO adducts at a S, C, N or O. See also the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 mailed to the United States Patent and Trademark Office on January 6, 1999.

Furthermore, WO 93/09806 does not describe any biological activity of any derivatized form of hemoglobin. Therefore, one of ordinary skill in the art would not only not know how to make a derivatized form of hemoglobin capable of delivering NO to tissues, but also would not know how to use such a derivatized form of hemoglobin, if it could be made.

One species of nitrosated hemoglobin that had been characterized at the time of the invention was nitrosylhemoglobin, which has an NO adduct on the heme Fe. Nitrosylhemoglobin, having NO bound at the heme Fe instead of having $O_2$ bound, is useless for carrying oxygen and is nowhere reported in the prior art as being a donor of NO. Thus, one of ordinary skill in the art would think it useless for any "method for potentiating delivery of NO to tissues in a mammal" as called for in Claim 16. One of ordinary skill in the art would have no reason to use nitrosylhemoglobin alone or in any combination in the method of Claim 16, where the objective is to regulate delivery of oxygen and NO in a mammal.

Applicants have shown that nitrosylhemoglobin can be converted under physiological conditions in the lung to SNO-hemoglobin. See Example 15, "Conversion of Nitrosylhemoglobin to SNO-Hemoglobin," page 72, line 21 to page 73, line 8, and Example 18, "Role of β93Cys in Destabilizing Nitrosyl-Heme," page 75, lines 5-28, and page 28, line 34 to page 29, line 15. This conversion process was previously unknown.

Unmodified purified hemoglobin has been administered alone as a carrier of oxygen, and is known to be a vasoconstrictor. See, for example, Feola *et al.*, (US 5,439,882) last sentence of column 4: "On the one hand, experimental observations have been reported of a vasoconstrictor effect of Hb."

One combination in the method of Claim 16 is hemoglobin plus a low molecular weight thiol. This combination is not discussed or implied for any purpose in WO 93/09806. A low molecular weight thiol is brought up in a description of a method to thiolate a protein (see page 22, lines 24-29 of WO 93/09806), and in a method to produce S-nitrosothiols (page 2, lines 6-9) but in no other context.

Another combination in the method of Claim 16 is nitrosated hemoglobin and low molecular weight thiol. This combination is not discussed or implied for any purpose in WO 93/09806. As discussed above, a low molecular weight thiol is brought up in a description of a method to thiolate a protein (see page 22, lines 24-29 of WO 93/09806) and in a method to produce S-nitrosothiols, but in no other context. No role is discussed for any possible enhancement of the effects of a nitrosated hemoglobin by a low molecular weight thiol.

The Examiner states:

> Further it is known in the art that hemoglobin is involved in regulating oxygen metabolism by its ability to bind reversibly to blood oxygen and thus facilitate the capability of blood to transport oxygen to bodily tissues (e.g. see bottom of page 19 - top of page 20). Accordingly, it would have been obvious to combine a low molecular weight thiol or nitrosothiol with either hemoglobin or nitrosated hemoglobin to deliver oxygen or NO (e.g. claim 16) since the Stamler reference teaches the use of the same compounds separately to effectuate the same function.

Nowhere does WO 93/09806 teach or suggest that low molecular weight thiols are involved in regulating oxygen metabolism, either by themselves or in combination with anything else. Nowhere does WO 93/09806 teach or suggest any combination of a low molecular weight thiol with hemoglobin or a nitrosated hemoglobin for any enhanced effect of NO delivery or any other reason. No additive effect is taught and no intermolecular interaction is taught that could suggest any additive effect.

The Examiner states, "In the present instance the reference provides motivation to combine hemoglobin's blood oxygen transport properties with the complementary benefits imparted by an NO-donating protein." This reasoning is not understood, as a low molecular weight thiol is not an NO-donating protein. Low molecular weight thiols do not have NO.

Claims 20-22, 27 and 28

Claims 20-22, 27 and 28 are all drawn to methods of treating a mammal (a human patient in Claims 27 and 28), comprising administering to the mammal nitrosated hemoglobin (or nitrated hemoglobin, in the case of Claim 21). Nitrosated hemoglobins described in the written description of the application include SNO-hemoglobin and nitrosylhemoglobin, in which the NO adduct is on the Fe of the heme.

The Examiner states:

> Additionally, the use of Nitrosated/Nitrated proteins, including nitrosated/nitrated hemoglobin to deliver NO to tissues (e.g. claim 40) in order to effectuate the treatment of abnormalities or diseases which are mediated by nitric oxide and oxygen metabolism (e.g. lung disease, sickle cell anemia, heart disease, high blood pressure etc.) would have been obvious since the reference discloses the use of nitrosated proteins, including nitrosated hemoglobin, to treat such disease states.

The WO 93/09806 reference discloses the making of some S-nitroso derivatives of proteins that can be produced by reaction with acidified nitrite, and specific effects of those derivatives: platelet aggregation, relaxation of smooth airway muscle, and vasodilation. As explained in previous Amendments, S-nitrosohemoglobin cannot be made using acidified nitrite, and insufficient support for any other method of synthesis of S-nitrosohemoglobin is presented in WO 93/09806. Any effects of SNO-hemoglobin reported in WO 93/09806 are mere speculation.

The Examiner states, "Additionally, applicants fail to appreciate the reference teaching as a whole in which the reference teaching of a nitrosylated/nitrosated hemoglobin genus would include nitrosylhemoglobin; which is in fact mentioned on page 58, lines 19-21 of WO 93/09806 as acknowledged by applicant." It has been acknowledged by Applicants that the word "nitrosyl-hemoglobin" appears at that location. There, the authors of WO 93/09806 attempt to produce nitrosylhemoglobin merely to compare the UV spectrum of this species with the UV spectrum of

the hemoglobin species they were hoping was S-nitrosohemoglobin. It is unknown from the description on page 58 what species of hemoglobin were actually produced. WO 93/09806 does not present an enabling description of any method of therapy using nitrosylhemoglobin. No evidence of any biological activity of nitrosylhemoglobin is presented. Such evidence is necessary for the enablement of any method of nitrosylhemoglobin in which it is to act as a donor of NO. All studies on nitrosylhemoglobin prior to the invention by Applicants concluded that it cannot carry oxygen and it does not act as a carrier or donor of NO.

Applicants have previously presented extensive explanation of the content of WO 93/09806, and have argued that it does not present an enabling description of a method to produce S-nitrosohemoglobin. No evidence was ever presented in WO 93/09806 that the molecule was made in any detectable amount, and no biological effects of S-nitrosohemoglobin were demonstrated.

A telephonic interview was held on February 13, 2001, in which the attorney Carol Egner and the inventor Jonathan Stamler discussed issues with the Examiner, Bennett Celsa. Based on the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 filed on 6 January 1999 and exhibits accompanying the Declaration, the Examiner stated that he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin. There remained a question of whether other species of nitrosated hemoglobin could have been produced from methods described in WO 93/09806. It was presented to the Examiner that it would be very unlikely that NO adducts were produced at O, N or C atoms in the hemoglobin molecule, if none could be detected at S atoms, because the thiol groups were the most reactive nucleophilic sites. The product of the method of WO 93/09806 was oxidized at the heme (methemoglobin). WO 93/09806 does not present a method to use nitrosylhemoglobin as a donor of NO in therapy. Before the invention by Applicants, nitrosylhemoglobin would not have been expected to be, or to be converted to, a donor of NO. WO 93/09806 does not present an enabling desciption of any method to use any nitrosated hemoglobin in therapy. Therefore, there is no basis for this rejection.

Claim 40

Claim 40 is drawn to a method for delivering NO or its biological equivalent to tissues in an animal or human, comprising administering to the animal or human an effective amount of one or more nitrosyl-heme-containing donors of NO.

The Examiner does not state what teachings of the reference render this method obvious. Nitrosyl-hemoglobin, which is one nitrosyl-heme-containing donor of NO, is mentioned on page 58, lines 19-21 of WO 93/09806, but is not mentioned as being useful in any method of therapy, or as being under any circumstances a carrier or donor of NO. It was not until the experiments described in Examples 15-18 (pages 72-75 of the written description) that it was known that nitrosylhemoglobin can be converted under physiological conditions in the lung to SNO-hemoglobin, which can be a donor of NO.

Rejection of Claim 41 Under 35 U.S.C. § 103(a) (Item 6 of Office Action)

Claim 41 has been rejected under 35 U.S.C. § 103(a), as it is said to be unpatentable over Stamler WO 93/09806 as applied to Claims 16, 20-22, 27, 28 and 40 above, and further in view of Moore *et al.* (*J. Biol. Chem. 251(9)*:2788-2794, 1976) or Sharma *et al.* (*J. Biol. Chem. 253(18)*:6467-6472, 1978).

The teachings of WO 93/09806 have been described above.

Sharma *et al.* (*J. Biol Chem. 253*:6467-6472, 1978) describe experiments to measure the rate of dissociation of NO from nitrosylhemoglobin. The rate constant is on the order of $10^{-4}$ or $10^{-5}$, indicating that nitrosylhemoglobin is very stable, and hence, cannot donate NO or have any physiological effect of an NO donor. The Moore *et al.* (*J. Biol. Chem. 251(9)*:2788-2794, 1976) reference describes experiments on nitrosylhemoglobin and nitrosylmyoglobin (both produced from the respective deoxy molecules), in which dissociation of NO from these molecules is followed spectrophotometrically in the absence of oxygen. No studies of nitrosylhemoglobin and nitrosylmyoglobin are done under physiological conditions. Moore *et al.* find dissociation rate constants similar to those found by Sharma *et al.* The Moore *et al.* and Sharma *et al.* papers do not report or suggest any physiological effect of nitrosylhemoglobin or any other nitrosyl-heme containing NO donor. The low dissociation constant measured for nitrosylhemoglobin -- 1,000 times lower than that of CO and 200,000 times lower than that of oxygen, by comparison (see,

for example, Greenburg, A.G. and H.W. Kim, *Art. Cells, Blood Subs., and Immob. Biotech. 23*:271-276, 1995, especially fifth paragraph on page 272; reference AX) – would lead one of ordinary skill in the art to conclude that nitrosylhemoglobin cannot be a donor of NO and that nitrosylhemoglobin could have no physiological effect because of the extremely low rate of release of NO from hemoglobin.

The Examiner states,

> The Stamler reference although disclosing the use of nitrosyl-heme containing NO donors to deliver NO or its biological equivalent to tissues (e.g. present claim 40) fails to specifically disclose the use of nitrosylhemoglobin (e.g. dependent claim 41). However, nitrosylhemoglobin compositions are conventionally known in the art. E.g., see the Moore and Sharma references. Additionally, the Stamler reference specifically addresses nitrosylhemoglobin on page 58. One of ordinary skill in the art would be motivated to select nitrosylhemoglobin to deliver NO to tissues in view of the Stamler reference which suggests that this compound would be expected to function as an NO-donating compound.

The Stamler reference WO 93/09806 discusses SNO- derivatives of certain proteins, produced by reaction of the proteins with acidified nitrite [e.g., cathepsin, bovine serum albumin (BSA), tissue plasminogen activator (tPA)]. The reference postulates the production of SNO-hemoglobin. None of these are nitrosyl-heme containing donors of NO. A nitrosyl-heme has NO bound to the Fe in the heme. The reference briefly mentions nitrosyl-hemoglobin on page 58, lines 19-21, but nowhere does it discuss nitrosyl-hemoglobin or any nitrosyl-heme-containing compound as being a donor of NO or its biological equivalent. As the Examiner points out, WO 03/09806 ". . . specifically addresses nitrosylhemoglobin on page 58." There is exactly one sentence addressing nitrosylhemoglobin, reproduced here: "For the purposes of comparison, equimolar concentrations of hemoglobin and $NaNO_2$ were reacted in 0.5 N HCl, to form nitrosyl-hemoglobin, and the UV spectrum was obtained." This sentence does allow for the conclusion, as the Examiner states, "One of ordinary skill in the art would be motivated to select nitrosylhemoglobin to deliver NO to tissues in view of the Stamler reference which suggests that this compound would be expected to function as an NO-donating compound." The Stamler reference does not say anything about nitrosylhemoglobin functioning as an NO-donating compound or having any biological activity.

Nitrosylhemoglobin is known in the art. However, nowhere in the prior art is nitrosylhemoglobin described as being a donor of NO, or as being useful in any method of therapy. One of ordinary skill in the art, presented with the teachings of WO 93/09806 and Moore *et al.* or Sharma *et al.*, would know how to produce nitrosylhemoglobin in the laboratory, but would know from the teachings of Sharma *et al.* and from other prior art that NO is very tightly bound to the heme Fe, and that nitrosylhemoglobin could not be useful as an NO donor. It was only with the experiments described in Examples 15 and 18 of the subject written description, for example, that it was discovered that nitrosylhemoglobin is converted in the lung to SNO-hemoglobin which is, in fact, a donor of NO.

Rejection of Claims 11-15 Under 35 U.S.C. § 103(a) (Item 7 of Office Action)

Claims 11-15 have been rejected under 35 U.S.C. § 103(a), as they are said to be unpatentable over Stamler *et al.* (WO 93/09806).

Claim 13 was canceled with an Amendment mailed to the United States Patent and Trademark Office on 31 October 2000.

WO 93/09806 describes a method for producing SNO-hemoglobin. However, this method is described so incompletely that one of ordinary skill in the art could not follow the protocol. No method of assay is described that could measure whether any SNO-hemoglobin had been formed. The method is merely hypothetical; no evidence is given that SNO-hemoglobin was actually produced, and no physiological effect of SNO-hemoglobin was measured. See the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 mailed to the United States Patent and Trademark Office on January 6, 1999. See Example 19 on pages 58-59 of WO 93/09806.

The Examiner states,

> It is further noted that the use of higher pH values (e.g. pH 7.4) than that utilized in the thionitrosylated hemoglobin example (e.g. pH 6.9 Example 19) is also suggested by the reference since thionitrosylated proteins are known to be stable under physiological conditions (e.g. TBS, pH 7.4, room temperature: see page 31) and further the reference discloses the use of pH 7.4 in the making and storage of various thiol proteins. Additionally, the

thiol-protein synthetic steps are analogous to that of Example 19: see page 30, lines 20-27; page 33, lines 20-26).

The reported stability of S-NO-t-PA at pH 7.4 does not reveal anything about the reaction conditions under which it can be made. WO 93/09806 does not disclose "the use of pH 7.4 in the steps analogous to that of Example 19." On page 30, lines 20-27 (also on page 33, lines 20-26, for bovine serum albumin) of WO 93/09806 is reported a 3-step process:

Step 1: "t-PA was first dialyzed against *a large excess of 10 mM HCl* for 24 hours to remove excess L-arginine used to solubilize the protein." HCl is a strong acid. This step occurs at a pH much lower than 7.4.

Step 2: "t-PA was then exposed to $NO_x$ generated from equimolar $NaNO_2$ in *0.5 N HCl (acidified $NaNO_2$)* or in control experiments, *to 0.5 N HCl alone*, for 30 minutes at 37°C." This second step is the step in which the nitrosylation occurs. HCl is used in both experimental and control conditions for the reaction. HCl is a strong acid. This step occurs at a pH much lower than 7.4 – probably about pH 2.

Step 3: "Solutions were titrated to pH 7.4 with equal volumes of 1.0 N NaOH and Tris Buffered Saline (TBS), pH 7.4, 0.05 M L-arginine." After the reaction has occurred under acidic conditions, the pH is raised to 7.4 using 1.0 N NaOH, a strong base. No reaction occurs at pH 7.4; no "$NO_x$" is generated from $NaNO_2$ at pH 7.4.

One of ordinary skill in the art would know that proteins are denatured at pH 2, and that hemoglobin subjected to pH 2 is dissociated into subunits and no longer exists as hemoglobin, having lost all capacity to function as an oxygen carrier.

The Examiner summarizes the arguments previously presented: "Applicant argues that the reference example for making S-nitrosylated hemoglobin (e.g., Example 19) teaches using pH of 6.9 and the reference fails to exemplify the making of S-nitrosylated hemoglobin at pH of 7.4 or higher." Applicants have argued that the reference does not teach making S-nitrosylated hemoglobin at any pH.

Applicants wish to remind the Examiner of his stated conclusion in a telephonic interview in which he discussed issues with attorney Carol Egner and inventor Jonathan Stamler on 13 February 2001. The Examiner stated, that based on the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 filed on 6 January 1999 and exhibits accompanying the

Declaration, he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin.

Rejection of Claims 17-19, 29, 69, 72 and 81 Under 35 U.S.C. § 103(a) (Item 8 of Office Action)

Claims 17-19, 29, 69, 72 and 81 have been rejected under 35 U.S.C. § 103(a), as they are said to be unpatentable over Feola *et al.*, U.S. Patent No. 5,439,882 and Stamler *et al.* (WO 93/09806), and, "if necessary," further in view of Moore *et al.* (*J. Biol. Chem. 251(9)*:2788-2794, 1976 or Sharma *et al.* (*J. Biol. Chem. 253(18)*:6467-6472, 1978).

Feola *et al.* (US 5,439,882) describe a cross-linked mammalian hemoglobin, a method of making the same, and a method of using the same as a blood substitute. Reduced glutathione, a thiol that occurs naturally in red blood cells, is used in the method of synthesis to stop the cross-linking of hemoglobin when using O-adenosine as a cross-linking agent; in this case glutathione reacts through its amine group to become cross-linked to a second glutathione molecule or to become cross-linked to hemoglobin. *Excess glutathione is dialyzed out, so that the cross-linked hemoglobin composition contains no free low molecular weight thiol.* See column 13, lines 2-6 and lines 27-30, and column 18, lines 62-64. Glutathione, in any case, is a low molecular weight thiol, not a low molecular weight *S-nitrosothiol*, as called for in the blood substitute of Claim 18. Feola *et al.* do not suggest any advantage for including any S-nitrosothiol in a blood substitute, nor do the other cited references. The hemoglobin composition of Feola contains no nitrosated or nitrated hemoglobin, and no low molecular weight S-nitrosothiol at all. Feola *et al.* do not teach or suggest any form of nitrosated hemoglobin or suggest any advantage for it, or for the addition of a low molecular weight S-nitrosothiol. Nor do Feola *et al.* teach or suggest any form of a nitrosyl-heme-containing donor of NO, such as nitrosyl-hemoglobin.

The teachings of Stamler *et al.* (WO 93/09806) have been described above. Applicants wish to remind the Examiner of his stated conclusion in a telephonic interview in which he discussed issues with attorney Carol Egner and inventor Jonathan Stamler on 13 February 2001. The Examiner stated, that based on the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 filed on 6 January 1999 and exhibits accompanying the Declaration, he had

accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin.

Sharma *et al.* (*J. Biol. Chem. 253*:6467-6472, 1978) describe experiments to measure the rate of dissociation of NO from nitrosylhemoglobin. The rate constant is on the order of $10^{-4}$ or $10^{-5}$, indicating that nitrosylhemoglobin is very stable, and hence, cannot donate NO or have any physiological effect of an NO donor. The Moore *et al.* reference (*J. Biol. Chem. 251(9)*:2788-2794, 1976) describes experiments on nitrosylhemoglobin and nitrosylmyoglobin (both produced from the respective deoxy molecules), in which dissociation of NO from these molecules is followed spectrophotometrically in the absence of oxygen. Moore *et al.* find dissociation rate constants similar to those found by Sharma *et al.* The Moore *et al.* and Sharma *et al.* papers do not report or suggest any physiological effect of nitrosylhemoglobin or any other nitrosyl-heme containing NO donor. The low dissociation constant measured for nitrosylhemoglobin -- 1,000 times lower than that of CO and 200,000 times lower than that of oxygen, by comparison (see, for example, Greenburg, A.G. and H.W. Kim, *Art. Cells, Blood Subs., and Immob. Biotech. 23*:271-276, 1995, especially fifth paragraph on page 272; reference AX) – would lead one of ordinary skill in the art to conclude that nitrosylhemoglobin cannot be a donor of NO and that nitrosylhemoglobin could have no physiological effect because of the extremely low rate of release of NO from hemoglobin.

Blood substitutes are known in the prior art, but none containing a nitrosated or nitrated derivative of hemoglobin. The administration of blood substitutes to a human or other mammal to restore blood volume and restore capacity for carrying oxygen is known. An effect of hemoglobin-based blood substitutes has been vasoconstriction. See Feola *et al.*, last sentence of column 4. It is therefore desirable to limit any vasoconstrictive effect found in a hemoglobin-based blood substitute.

The Examiner states:

> The Stamler reference specifically discloses the use of nitrosylated proteins and low molecular weight nitrosating agents (e.g., see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (e.g., see pages 19-25 and claims).

The Stamler reference (WO 93/09806) discusses a method of producing SNO-hemoglobin which was unsuccessful, as the Examiner has concluded. The reference includes no data on physiological effects of SNO-hemoglobin, as no SNO-hemoglobin was produced. The Stamler reference does not teach any nitrosylated protein that increases oxygen capacity and transport and modulates CO; no evidence of these properties is provided for any protein. No supporting data were presented that species of hemoglobin with NO adducts on C, N or O were produced. None of the other cited references teach these hemoglobin species. The Stamler reference does not state or imply that nitrosylhemoglobin can be a donor of NO. Neither do any of the other cited references. None of the cited references, alone or in combination, teach a SNO-hemoglobin or a nitrosylated hemoglobin species that has properties sought for a blood substitute.

The Stamler reference (WO 93/09806) discussed certain effects of other SNO-proteins that were produced by a method using acidified nitrite. There was nothing about these reported effects of the SNO-proteins that could have suggested the effects observed with SNO-hemoglobin when it was ultimately made and tested. Unlike the SNO-proteins described in the Stamler reference, which act as vasodilators, SNO-hemoglobin is not in every case a vasodilator, and can be a vasoconstrictor in some cases. See, for example, page 17, lines 17-29, page 19, lines 12-25, page 57, line 3 to page 58, line 2 and Figure 4A.

One of ordinary skill in the art might have wanted to use SNO-oxyhemoglobin, if it could be made, as a component of a blood substitute for its expected oxygen carrying capacity and its expected vasodilatory effects, based on the reported effects of other SNO-proteins as NO donors. However, one of ordinary skill in the art could not have predicted from the teachings of Stamler or from any combination of the cited references that SNO-hemoglobin could have the opposite --

that is, a vasoconstrictive -- effect, and therefore would not be desirable in methods of therapy in which vasoconstriction is undesirable (e.g., cardiovascular disorders or respiratory disorders as mentioned in Stamler *et al.*).

The Examiner states, "Further, nitrosylated hemoglobin preparations, e.g., nitrosylhemoglobin compositions, are conventionally known in the art. E.g., see the Moore and Sharma references." It is true that nitrosylhemoglobin was known. However, it was known to have a very high affinity for NO, and therefore would not be suspected of ever being a donor of NO itself, and would not be suspected of being converted to SNO-hemoglobin, which is a donor of NO. Nothing in the prior art suggests this conversion process.

Combining the teachings of Stamler *et al.* and Feola *et al.*, one of ordinary skill in the art might seek to use SNO-hemoglobin in a blood substitute, to deliver oxygen and NO, but would not know how to make it from Example 19 of Stamler *et al.*, and would be unable to combine it with a low molecular weight S-nitrosothiol, as in Claim 18. If one of ordinary skill in the art could obtain a sample of SNO-hemoglobin, he would be surprised that in the oxyhemoglobin form, SNO-hemoglobin would cause vasoconstriction, unlike other SNO-proteins. One of ordinary skill in the art would have no reason based on anything found in the cited references, including Moore *et al.* and Sharma *et al.*, to think of including nitrosylhemoglobin in a blood substitute, as nitrosylhemoglobin was not known to have any physiological effect, including the intended effect of a blood substitute, carrying oxygen. It was unknown until the subject application that nitrosylhemoglobin could be converted in the lung to SNO-hemoglobin, a donor of NO. See, for instance, Example 15, page 72, line 21 to page 73, line 8, Example 18, page 75, lines 5-28, and page 28, line 34 to page 29, line 5.

Feola *et al.* (U.S. 5,439,882) teach a cross-linked hemoglobin to be used as a blood substitute. Feola *et al.* do not teach any method to deliver NO in a mammal, and do not teach nitrosated hemoglobin. Stamler *et al.* (WO 98/09806) do not teach any form of nitrosylated hemoglobin with any biological activity, as they give no evidence of any hemoglobin derivative with any ability to carry oxygen or to deliver NO. Moore *et al.* and Sharma *et al.* describe nitrosylhemoglobin as having NO so tightly bound to the heme iron so as to be useless in carrying oxygen.

Combining these teachings, one of ordinary skill in the art would not know how to make any nitrosated or nitrated derivative of hemoglobin capable of carrying oxygen. One of ordinary skill in the art would be discouraged from trying to make SNO-hemoglobin to use as a blood substitute, as no evidence of its synthesis or physiological effects is given in WO 93/09806. One certainly would not include nitrosylhemoglobin in a blood substitute, as it is taught by Moore *et al.* and Sharma *et al.* that nitrosylhemoglobin cannot carry oxygen. S-nitrosothiol is taught by Stamler *et al.* as having vasodilation activity. One of ordinary skill in the art might wish to combine these with the blood substitute of Feola *et al.*

Rejection of Claims 11, 12, 14-22, 27-29, 40, 41, 43, 44, 46, 63, 65, 69, 72 and 81 Under the Doctrine of Obviousness-Type Double Patenting (Item 9 of Office Action)

Claims 11, 12, 14-22, 27-29, 40, 41, 43, 44, 46, 63, 65, 69, 72 and 81 have been rejected under the doctrine of obviousness-type double patenting. The Examiner states that the recited claims of this application conflict with claims which are present in Application No. 08/667,003 and Application No. 08/796,164.

Application No. 09/667,003 issued as US Patent No. 6,197,745 on March 6, 2001. Application No. 08/796,164 is the subject of this Office Action.

Applicants wish to remind the Examiner that on 6 January 1999, two Terminal Disclaimers were mailed to the United States Patent and Trademark Office -- one relating to Application No. 09/667,003 (now US Patent No. 6,197,745), the other relating to Application No. 08/616,371 (still pending).

Rejection of Claims 69 and 72 Under 35 U.S.C. § 102(e,f), or Alternatively, Under 35 U.S.C. § 103 (Item 12 of Office Action)

Claims 69 and 72 have been rejected "under 35 U.S.C. § 102(e,f) as being anticipated by" or alternatively, "under 35 U.S.C. § 103 as being obvious over Stamler *et al.*" (US Patent No. 6,291,424). It is assumed that by "35 U.S.C. § 102(e,f)," the Examiner means 35 U.S.C. § 102(e) or 35 U.S.C. § 102(f) as alternative theories for anticipation.

The teachings of Stamler *et al.* (US Patent No. 6,291,424) are those of WO 93/09806, which teachings have been described above. Applicants wish to remind the Examiner of his

stated conclusion in a telephonic interview in which he discussed issues with attorney Carol Egner and inventor Jonathan Stamler on 13 February 2001. The Examiner stated, that based on the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 filed on 6 January 1999 and exhibits accompanying the Declaration, he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin.

In this case, there can be no conception without reduction to practice. That is, one might think that a hemoglobin molecule with NO adduct(s) on one or more thiols of the cysteine residues might be possible in theory. However, carrying out any chemical modification on a protein is difficult to do without denaturing the protein, and particularly difficult on a protein that must maintain exact conformations to be able to bind and unload oxygen from the heme in response to the appropriate environmental conditions. There was no demonstration in WO 93/09806 or in US Patent No. 6,291,424 that any amount of SNO-hemoglobin was ever produced. Therefore, there was no invention of SNO-hemoglobin by the people named as inventors on US Patent No. 6,291,424. No invention could have been derived from the people named as inventors on US Patent No. 6,291,424, as there is no indication that they ever had possession of knowledge to make SNO-hemoglobin.

With regard to possible obviousness of the subject matter of Claims 69 and 72, US Patent No. 6,291,424 teaches methods of producing a few SNO-proteins, for example, derivatives of bovine serum albumin, cathepsin B, immunoglobulin and tissue plasminogen activator. These proteins were subjected to acidified $NaNO_2$ (equimolar $NaNO_2$ in 0.5 N HCl) and became denatured by the strong acid. The SNO-proteins were not tested for any enzymatic function or any other activity that would indicate their conformational state following strong acid treatment. The strong acid procedure does not teach or suggest a method to produce SNO-hemoglobin. As discussed above, the procedure of Example 19 in US Patent No. 6,291,424 does not rise to the level of teaching or suggesting a procedure that instructs one of ordinary skill in the art in a method of producing SNO-hemoglobin. As demonstrated in the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 filed on 6 January 1999 and exhibits accompanying the Declaration, the method described in Example 19 is incomplete and inoperable.

Rejection of Claims 21, 22, 27, 28, 40, 41, 69 and 72 Under 35 U.S.C. § 102(e,f), or Alternatively, Under 35 U.S.C. § 103 (Item 13 of Office Action)

Claims 21, 22, 27, 28, 40, 41, 69 and 72 have been rejected "under 35 U.S.C. § 102(e,f) as being anticipated by" or alternatively, "under 35 U.S.C. § 103 as being obvious over Stamler *et al.*" (US Patent No. 6,583,113). It is assumed that the Examiner means 35 U.S.C. § 102(e) or 35 U.S.C. § 102(f) as alternative theories for anticipation.

US Patent No. 6,583,113 issued on a divisional of the patent application that issued as US Patent No. 6,292,424. Thus, the content of the two patents is the same, except for the issued claims.

Claims 21, 22, 27 and 28

Claims 21, 22, 27 and 28 are drawn to methods of treating a disease or medical condition in a mammal or human patient, comprising administering nitrosated or nitrated hemoglobin. There is no evidence presented in US Patent No. 6,583,113 that any form of nitrosated or nitrated hemoglobin has any biological activity that can be applied to any disease or medical condition. There is nothing in US Patent No. 6,583,113 that indicates that any form of nitrated or nitrosated hemoglobin can be produced. Nitrosyl-hemoglobin is only mentioned in column 30, lines 13-17. The experimenters attempted to produce nitrosyl-hemoglobin to use as a standard for comparison of its UV spectrum. No therapeutic qualities of nitrosyl-hemoglobin are discussed or implied in US Patent No. 6,583,113. No person of ordinary skill in the art could infer from the teachings of US Patent No. 6,583,113 that a nitrosated or nitrated hemoglobin could be produced that would be useful in a method of therapy. One of ordinary skill in the art would conclude from Example 19 of 6,583,113 that the synthesis of SNO-hemoglobin failed. Because the applicants listed for US Patent No. 6,583,113 were not the first to invent, and did not have in their possession any invention of a method of treating a disease or medical condition in a mammal or human patient, comprising administering nitrosated or nitrated hemoglobin, they could not have conveyed any information on an invention to anyone else.

With regard to possible obviousness of the subject matter of Claims 21, 22, 27 and 28, U.S. 6,583,113 does not teach any physiological effect of a nitrosated or nitrated hemoglobin. U.S. 6,583,113 contains insufficient teaching for one of ordinary skill in the art to conclude that

any derivative of hemoglobin was produced. Therefore, it would not be obvious to one of ordinary skill in the art that nitrosated or nitrated hemoglobin could be made or that it could be used for any method of therapy.

Claims 40 and 41

Claims 40 and 41 are drawn to methods for delivering NO or its biological equivalent to tissues in an animal or human, comprising administering to the animal or human an effective amount of one or more nitrosyl-heme-containing donors of NO.

US Patent No. 6,583,113 does not teach anything about nitrosyl-heme containing molecules being administered to an animal or human for any purpose. Nitrosyl-hemoglobin is only mentioned in column 30, lines 13-17. In Example 19 of 6,583,113, the experimenters attempted to produce nitrosyl-hemoglobin to obtain its UV spectrum. No therapeutic qualities of nitrosyl-hemoglobin or any other nitrosyl-heme molecule are discussed in US Patent No. 6,583,113. Because the applicants listed for US Patent No. 6,583,113 were not the first to invent, and did not have in their possession any invention of a method for delivering NO or its biological equivalent to tissues in an animal or human, comprising administering to the animal or human an effective amount of one or more nitrosyl-heme-containing donors of NO, they could not have conveyed any invention to anyone else.

Regarding possible obviousness of the subject matter of Claims 40 and 41, U.S. 6,583,113 does not suggest that nitrosyl-hemoglobin or nitrosyl-heme-containing donors of NO in general are useful in any method of therapy. One of ordinary skill in the art would not conclude from the use of nitrosyl-hemoglobin described in U.S. 6,583,113 that it is a donor of NO. Nitrosyl-hemoglobin was merely used as a reference for its absorbance spectrum. No person of skill in the art would even be encouraged to test nitrosyl-hemoglobin to see if it could be a donor of NO. Papers describing studies of nitrosyl-hemoglobin conclude that NO has an extremely high affinity for heme Fe, and U.S. 6,583,113 contains nothing to contradict this conclusion.

Claims 69 and 72

The teachings of Stamler *et al.* (US Patent No. 6,583,113) are those of WO 93/09806, which teachings have been described above. Applicants wish to remind the Examiner of his stated conclusion in a telephonic interview in which he discussed issues with attorney Carol Egner and inventor Jonathan Stamler on 13 February 2001. The Examiner stated, that based on the Declaration of Jonathan S. Stamler, M.D. Under 37 C.F.R. § 1.132 filed on 6 January 1999 and exhibits accompanying the Declaration, he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin.

In this case, there can be no conception without reduction to practice. That is, one might think that a hemoglobin molecule with NO adduct(s) on one or more thiols of the cysteine residues might be possible in theory. However, carrying out any chemical modification on a protein is difficult to do without denaturing the protein, and particularly difficult on a protein that must maintain exact conformations to be able to bind and unload oxygen from the heme in response to the appropriate environmental conditions. There was no demonstration in WO 93/09806 or in US Patent No. 6,583,113 that any amount of SNO-hemoglobin was ever produced. Therefore, there was no invention of SNO-hemoglobin by the people named as inventors on US Patent No. 6,583,113. No invention could have been derived from the people named as applicants on US Patent No. 6,583,113, as there is no indication that they ever had possession of knowledge to make SNO-hemoglobin.

With regard to possible obviousness of the subject matter of Claims 69 and 72, US Patent No. 6,583,113 teaches methods purported to produce a few SNO-proteins, for example, bovine serum albumin, cathepsin B, immunoglobulin and tissue plasminogen activator. These proteins were subjected to acidified $NaNO_2$ (equimolar $NaNO_2$ in 0.5 N HCl) and became denatured by the strong acid. The SNO-proteins were not tested for any enzymatic function or any other activity that would indicate their conformational state following strong acid treatment. The strong acid procedure does not teach or suggest a method to produce SNO-hemoglobin. As discussed above, the procedure of Example 19 in US Patent No. 6,583,113 does not rise to the level of teaching or suggesting sufficient instruction for one of ordinary skill in the art to produce SNO-hemoglobin. As demonstrated in the Declaration of Jonathan S. Stamler, M.D. Under 37

C.F.R. § 1.132 filed on 6 January 1999 and exhibits accompanying the Declaration, the method described in Example 19 is incomplete and inoperable.

Rejection of Claims 16-22, 27-29, 40, 41, 69, 72 and 81 Under 35 U.S.C. § 102(e,f), or Alternatively, Under 35 U.S.C. § 103 (Item 14 of Office Action)

Claims 16-22, 27-29, 40, 41, 69, 72 and 81 have been rejected under 35 U.S.C. § 102(e,f), as they are said to be anticipated by, or alternatively, under 35 U.S.C. § 103, as they are said to be obvious over Stamler *et al.* (US Patent No. 6,471,978).

Stamler *et al.* (US Patent No. 6,471,978) describe medical devices coated with a nitric oxide adduct. Among the nitric oxide adducts recited for use in the medical devices are S-nitroso-proteins. US Patent No. 6,471,978 describes methods of producing S-nitroso-proteins at column 19, lines 6-19. However, one of ordinary skill in the art would not be able to make and use S-nitroso-hemoglobin or any other form of nitrosated or nitrated hemoglobin based on these described methods. One of ordinary skill in the art would have no reason to think that any nitrosated or nitrated form of hemoglobin could be made. No information on the stability of any hemoglobin derivative is given, or on its suitability to being used as a coating for a medical device. No person of ordinary skill in the art would be able to produce the compositions of Claims 69, 72 and 81 or carry out any of the methods of Claims 16-22, 27, 28, 40 and 41 by looking for guidance from US Patent No. 6,471,978, as it does not have sufficient teachings regarding hemoglobin for anyone to be able to perform any chemical reaction to make any derivatized form of hemoglobin. Further, 6,471,978 does not have any experimental evidence regarding the biological activity of hemoglobin that has been nitrosated or nitrated. No invention could have been derived from the people named as inventors on US Patent No. 6,471,978, as there is no indication that they ever had possession of sufficient knowledge to produce the compositions of Claims 29, 69, 72 and 81, or to practice the methods of Claims 16-22, 27, 28, 40 and 41.

The Examiner states, without citing a specific location in US Patent No. 6,471,978, "Additionally, the reference teaches the combination of S-nitrosothiols with hemoglobin for their expected NO donating properties thus anticipating or rendering obvious present claims directed to 'potentiation of NO delivery.'" Claim 16 is directed to a method for potentiating delivery of

NO to tissues in a mammal, comprising administering to the mammal an effective amount of a mixture of a low molecular weight thiol and hemoglobin or nitrosated hemoglobin. US Patent No. 6,471,978 does not teach or suggest administering either a combination of a low molecular weight thiol and hemoglobin or nitrosated hemoglobin, as called for in Claim 16, or a combination of S-nitrosothiols with hemoglobin, as the Examiner suggests.

One of ordinary skill in the art who studies US Patent No. 6,471,978 might think of hemoglobin as a candidate protein to be modified to a SNO-derivative. However, one intending to make the compositions of Claims 29, 69, 72 or 81, or to produce a derivative of hemoglobin with any of the activities required to carry out the methods of Claims 16-22, 27, 28, 40 and 41 would not be able to find a procedure to produce such a derivative -- in 6,471,978 or in any other publication existing at the time the priority application for the subject application was filed. US Patent No. 6,471,978 does not contain an enabling description of how to make any kind of derivative of hemoglobin -- nitrosated, nitrated, or otherwise. Nothing in the prior art combined with 6,471,978 makes up for this deficiency. Therefore, the methods of Claims 16-22, 27, 28, 40 and 41, and the compositions of Claims 29, 69, 72 and 81 cannot be obvious.

Rejection of Claims 69 and 72 Under Obviousness-Type Double Patenting (Item 16 of Office Action)

Claims 69 and 72 have been rejected under the judicially created doctrine of obviousness-type double patenting, as they are said to be unpatentable over Claims 1-6 of US Patent No. 6,291,424.

The inventors listed on the face of US 6,291,424 are Johnathan (*sic*) Stamler, Joseph Loscalzo and David J. Singel. The United States Patent and Trademark Office erred in listing Jonathan Stamler as an inventor. The version of 37 C.F.R. § 1.63 in effect on June 5, 1998 (the date of filing the application that later became US 6,291,424) required:

> the oath or declaration must state that the person making the oath or declaration:
>
> (1) Has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration;

> (2) Believes the named inventor or inventors to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought; and
> (3) Acknowledges the duty to disclose to the Office all information known to the person to be material to patentability as defined in § 1.56.

These are the only requirements to obtaining a valid signature by the inventors on a Declaration of Inventorship. The file history of US 6,291,424 is currently unavailable. However, the file history of US 6,583,113 has been studied. It contains copies of some papers filed in US 6,291,424 (Patent Application No. 09/092,622), the parent to US 6,583,113. Papers submitted as exhibits with a Petition Under 37 C.F.R. 1.47(a) and Declarations in Support of Filing Under 37 C.F.R. § 1.47(a) filed on December 30, 1998 for 09/092,622 show that Dr. Stamler did not sign a Declaration of Inventorship for the application that became US 6,291,424 (Patent Application No. 09/092,622), because he did not believe the named inventors to be the original and first inventors of the subject matter claimed in the application. See Exhibit P, a copy of "Declaration of Gretchen A. Rice in Support of Filing Under 37 C.F.R. § 1.47(a)" mailed to the United States Patent and Trademark Office on 30 December 1998 for Patent Application No. 09/092,622. Also see Exhibit Q (referred to as Exhibit G in the Declaration of Gretchen A. Rice) a copy of a letter from Maxim H. Waldbaum, Esq. of Sidley & Austin to Gretchen A. Rice, Esq., attorney of record for Patent Application No. 09/092,622. In spite of the clear language of 37 C.F.R. § 1.63, the Senior Legal Advisor/Special Program Law Office (Office of the Deputy Assistant Commissioner for Patent Policy and Projects) who issued a decision on the Petition Under 37 C.F.R. 1.47(a) granted the Petition and granted the application Rule 1.47(a) status.

The Senior Legal Advisor was apparently persuaded by the argument made by the attorney for applicants of 09/092,622 that its specification "is identical to the specification of USSN 07/943,835." Apparently, the attorney for applicants of 09/092,622 was referring to the written sections of the application excluding the claims. The claims are in fact part of the specification. Therefore, it is not true that the specification of the patent application that became US 6,292,424 is identical to the specification of its parent application, 07/943,835.

The attorney for applicants of 09/092,622 brings up repeatedly in the Declaration in Support of Filing Under 37 C.F.R. § 1.47(a) the fact that Dr. Stamler had previously executed an

assignment to Brigham and Women's Hospital for US Patent Application No. 07/943,835 in 1992. However, 37 C.F.R. § 1.63 does not recognize, and no other statute in patent law recognizes, any obligation that allegedly results from the signing of an assignment in a related application. The only requirements for inventors, according to 37 C.F.R. § 1.63, are (1), (2) and (3) above. Note that (2) requires that all named inventors believe the named inventor or inventors to be the original and first inventor or inventors *of the subject matter which is claimed and for which a patent is sought.*" The subject matter of the claims in 09/092,622 was different from the subject matter of the claims of prior applications. It should be noted that Application No. 09/092,622 (US 6,291,424) is listed on the face of the 6,291,424 patent as being a continuation-in-part of Application No. 08/409,720 (filed March 24, 1995), which is a continuation-in-part of 08/198,854 (filed February 17, 1994), which is a divisional of 07/943,835 (filed September 14, 1992). The filing of the 09/092,622 as a continuation-in-part rather than a continuation is an acknowledgment that its claims are different from those of previously filed applications to which it claims priority. The signing of the assignment in 07/943,835 should not carry any weight; it does not state anything about the signatory's belief as to who invented the subject matter of the claims.

Because Jonathan S. Stamler is not an inventor of Claims 1-6 of US Patent No. 6,291,424, there is no common inventor between the instant application and US Patent No. 6,291,424, and no double patenting rejection can apply.

Provisional Rejection of Claims 69 and 72 Under Obviousness-Type Double Patenting (Item 17 of Office Action)

Claims 69 and 72 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as they are said to be unpatentable over Claims 1-14 of copending US Application No. 09/835,038 (PG PUB US 2002/0052314 A1; May 2, 2002).

Jonathan S. Stamler has not signed a Declaration of Inventorship applying to US Application No. 09/835,038, and cannot be assumed to be an inventor of the claims of 09/835,038 from any other circumstances.

Because Jonathan S. Stamler is not an inventor of Claims 1-14 of US Patent Application No. 09/835,038, there is no common inventor between the instant application and US Patent Application No. 09/835,038, and no double patenting rejection can apply.

Provisional Rejection of Claims 19-22, 27-28, 40-41, 69 and 72 Under Obviousness-Type Double Patenting (Item 18 of Office Action)

Claims 19-22, 27-28, 40-41, 69 and 72 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting, as they are said to be unpatentable over Claims 1-17 and "especially claims 7-9 and 17" of copending US Application No. 10/216,865 (PG PUB US 2003/0007967 A1; January 9, 2003).

Jonathan S. Stamler has not signed a Declaration of Inventorship applying to US Application No. 10/216,865, and cannot be assumed to be an inventor of the claims of 10/216,865 from any other circumstances.

Because Jonathan S. Stamler is not an inventor of Claims 1-17 of US Patent Application No. 10/216,865, there is no common inventor between the instant application and US Patent Application No. 10/216,865, and no double patenting rejection can apply.

Rejection of Claims 21, 22, 27, 28, 40, 41, 69 and 72 Under Obviousness-Type Double Patenting (Item 19 of Office Action)

Claims 21, 22, 27, 28, 40, 41, 69 and 72 have been rejected under the judicially created doctrine of obviousness-type double patenting, as they are said to be unpatentable over Claims 1-4 of US Patent No. 6,583,113.

Applicants request that the Examiner consider the file history of the parent application to US 6,583,113 (US Patent Application No. 09/835,038), which is 09/092,622 (now US Patent No. 6,291,424). The inventors listed on the face of US 6,291,424 are Johnathan (*sic*) Stamler and Joseph Loscalzo. The United States Patent and Trademark Office erred in listing Jonathan Stamler as an inventor. 37 C.F.R. § 1.63 requires, *inter alia*:

> (a) An oath or declaration filed under § 1.51(b)(2) as a part of a nonprovisional application must:

(4) State that the person making the oath or declaration believes the named inventor or inventors to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought.

The file history of US 6,291,424 (specifically, papers submitted as exhibits with a Petition Under 37 C.F.R. § 1.47(a) and Declarations in Support of Filing Under 37 C.F.R. § 1.47(a) filed on December 30, 1998 for 09/092,622) shows that Dr. Stamler did not sign a Declaration of Inventorship for that application because he did not believe the named inventors to be the original and first inventors of the subject matter claimed in the application. See the enclosed Exhibit Q, letter of Maxim H. Waldbaum Esq. to Gretchen A. Rice, Esq. dated December 16, 1998 used as Exhibit G with the Declaration of Gretchen A. Rice filed for Application No. 09/092,622 (now US Patent No. 6,291,424) on December 30, 1998. However, in spite of the requirements of 37 C.F.R. § 1.63, the United States Patent and Trademark Office granted the Petition and granted the application Rule 1.47(a) status.

The Senior Legal Advisor who drafted the Decision on the Petition was apparently persuaded by the argument made by the attorney for applicants of 09/092,622 that its specification "is identical to the specification of USSN 07/943,835." Apparently, the attorney for applicants of 09/092,622 was referring to the written sections of the application excluding the claims. The claims are in fact part of the specification. Therefore, it is not true that the specification of the patent application that became US 6,292,424 is identical to the specification of its parent application, 07/943,835.

The attorney for applicants of 09/092,622 brought up repeatedly in the Declaration in Support of Filing Under 37 C.F.R. § 1.47(a) the fact that Dr. Stamler had previously executed an assignment to Brigham and Women's Hospital for US Patent Application No. 07/943,835 in 1992. However, 37 C.F.R. § 1.63 does not recognize, and no other statute in patent law recognizes any obligation that allegedly results from the signing of an assignment in a related application. Note that 37 C.F.R. § 1.63(a)(4) requires that all named inventors believe the named inventors to be the original and first inventors "*of the subject matter which is claimed and for which a patent is sought.*" The subject matter of the claims in 09/092,622 was different from the subject matter of the claims of prior applications. It should be noted that Application No.

09/092,622 (US 6,291,424) is listed on the face of the 6,291,424 patent as being a continuation-in-part of Application No. 08/409,720 (filed March 24, 1995), which is a continuation-in-part of 08/198,854 (filed February 17, 1994), which is a divisional of 07/943,835 (filed September 14, 1992). The filing of the 09/092,622 as a continuation-in-part rather than a continuation is an acknowledgment that its claims are different from those of previously filed applications to which it claims priority. The signing of the assignment in 07/943,835 should not carry any weight; it does not state anything about the signatory's belief as to who invented the subject matter of the claims.

Copies of the papers in the parent to US 6,583,113, Application No. 09/092,622 -- the Petition Under 37 C.F.R. § 1.47(a), Declarations in Support of Filing Under 37 C.F.R. § 1.47(a) and exhibits accompanying the Declarations -- were submitted with Patent Application No. 09/835,038 (Patent No. 6,583,113) upon its filing on April 16, 2001. Status as an application under 37 C.F.R. § 1.47(a) was again granted by the Patent Office to 09/835,038, thereby repeating the mistake in the parent application 09/092,622.

Because Jonathan S. Stamler is not an inventor of Claims 1-4 of US Patent No. 6,583,113, there is no common inventor between the instant application and US Patent No. 6,583,113, and no double patenting rejection can apply.

Furthermore, Claims 21, 22, 27, 28, 40, 41, 69 and 72 of the subject application are patentably distinct from, and nonobvious in view of Claims 1-4 of US Patent No. 6,583,113. None of Claims 1-4 of 6,583,113 are composition claims, as are Claims 69 and 72 of the subject application. Claims 1-4 of US 6,583,113 do not comprise a step of administering to a mammal or a human patient a nitrosated or nitrated hemoglobin, or a nitrosyl-heme-containing donor of NO. Claims 1-4 of 6,583,113 read on a process that occurs in nature, as SNO-hemoglobin occurs naturally in red blood cells. See Table 2 on page 66 of the specification of the subject application.

Rejection of Claims 16-22, 27-29, 40, 41, 69, 72 and 81 Under Obviousness-Type Double Patenting (Item 20 of Office Action)

Claims 16-22, 27-29, 40, 41, 69, 72 and 81 have been rejected under the judicially created doctrine of obviousness-type double patenting, as they are said to be unpatentable over Claims 1-65 of US Patent No. 6,471,978.

Section 804 of the MPEP gives guidance on determining whether a nonstatutory basis exists for double patenting rejection. Page 800-22 of the MPEP states:

> Any obviousness-type double patenting rejection should make clear:
>
> (A) The differences between the inventions defined by the conflicting claims -- a claim in the patent compared to a claim in the application; and
>
> (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent.

The Examiner has not made clear the differences between each of the rejected claims and each of the 65 claims of US Patent No. 6,471,978 to which each of the rejected claims are being compared, and the reasons why a person of ordinary skill in the art would conclude that the invention defined in each of rejected Claims 16-22, 27-29, 40, 41, 69, 72 and 81 is an obvious variation of the invention defined in each of claims 1-65 of the patent. The Examiner instead includes a general discussion of the teachings of the patent, not an analysis of the claims.

Claims 29, 69, 72 and 81 of the application at issue are drawn to compositions. The claims of US Patent No. 6,471,978 are all drawn to methods. It is not explained by the Examiner how a composition can be an obvious variation of a method. The scope and content of composition Claims 29, 69, 72 and 81 are plainly different from the scope and content of all of method Claims 1-65 of US Patent No. 6,471,978. The claimed subject matter of Claims 29, 69, 72 and 81 is certainly patentably distinct from the subject matter claimed in US Patent No. 6,471,978. Obviousness-type double patenting is not meant to apply to subject matter that is so obviously non-overlapping and in entirely different categories of subject matter.

Claim 16 of the present application is drawn to a method for potentiating delivery of NO to tissues in a mammal, comprising administering to the mammal an effective amount of a mixture of a low molecular weight thiol and hemoglobin or nitrosated hemoglobin. Applicants can find no claim among Claims 1-65 of US Patent No. 6,471,987 that suggests using a combination of low molecular weight thiol with either hemoglobin or nitrosated hemoglobin, for any purpose. Applicants request that the Examiner make specific reference to the claim that suggests the subject matter of Claim 16.

Claim 17 of the present application is drawn to a method for delivering NO in a mammal, comprising administering to the mammal an effective amount of a blood substitute comprising nitrosated hemoglobin. Applicants can find no claim among Claims 1-65 of US Patent No. 6,471,987 that suggests administering to a mammal an effective amount of a blood substitute comprising nitrosated hemoglobin. Applicants request that the Examiner make specific reference to the claim that suggests the subject matter of Claim 17. Methods that require the application of a nitric oxide adduct locally to a vascular surface in no way suggest a method that requires administering to a mammal a blood substitute in an amount effective to deliver NO. The physiological consequences of applying a nitric oxide adduct to a vascular surface cannot be extrapolated by one of ordinary skill in the art to using nitrosated hemoglobin as a blood substitute.

Claim 18 of the present application is drawn to a method for delivering NO in a mammal, comprising administering to the mammal an effective amount of a blood substitute comprising nitrosated hemoglobin and low molecular weight S-nitrosothiol. Applicants can find no claim among Claims 1-65 of US Patent No. 6,471,987 that suggests using a combination of low molecular weight S-nitrosothiol and nitrosated hemoglobin, for any purpose. Applicants request that the Examiner make specific reference to the claim that suggests the subject matter of Claim 18, and explain why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue is an obvious variation of the invention defined in one of Claims 1-65 in the patent.

Claims 19, 20, 22, 27 and 28 of the present invention are all methods of therapy in a mammal or a human patient, the method comprising administering to the mammal nitrosated hemoglobin. The methods of the cited patent are all methods comprising applying to a damaged

vascular surface a nitric oxide adduct. Applicants request that the Examiner make specific reference to the claim that suggests the subject matter of Claims 19, 20, 22, 27 and 28, and that he explain the reasoning as to how a person of ordinary skill in the art would conclude that the invention defined in Claims 19, 20, 22, 27 and 28 is an obvious variation of the invention claimed in the patent. Methods that require the application of a nitric oxide adduct locally to a vascular surface in no way suggest a method that requires administering to a mammal nitrosated hemoglobin to have the systemic effects described in Claims 19, 20, 22, 27 and 28. The physiological consequences of applying a nitric oxide adduct to a vascular surface cannot be extrapolated by one of ordinary skill in the art to therapies to produce the systemic effects of Claims 19, 20, 22, 27 and 28.

Claim 21 is a method for treating a disease in a mammal, comprising administering an effective amount of nitrosated or nitrated hemoglobin to the mammal, wherein the disease is selected from the group consisting of heart disease, brain disease, vascular disease, atherosclerosis, lung disease and inflammation. The claims of the cited patent are drawn to methods that call for the application of a nitric oxide adduct locally to a vascular surface. The claims of the cited patent are drawn narrowly, compared to Claim 21 of the subject invention. Treating a disease in a mammal with nitrosated or nitrated hemoglobin, where the disease may be heart disease, brain disease, vascular disease, artherosclerosis, lung disease or inflammation, is not an obvious variation of a method to treat a damaged vascular surface by applying a nitric oxide adduct to the surface. The cited patent does not refer to nitrated hemoglobin anywhere, and "nitric oxide adduct" is not defined as encompassing nitrated hemoglobin.

Claims 40 and 41 are drawn to methods for delivering NO or its biological equivalent to tissues in an animal or human, comprising administering to the animal or human an effective amount of one or more nitrosyl-heme-containing donors of NO. The nitrosyl-heme-containing donor of NO can be nitrosylhemoglobin. Applicants can find no reference to a nitrosyl-heme-containing donor of NO in any of Claims 1-65 of US Patent No. 6,471,987 or anyplace else in US Patent No. 6,471,987. Therefore, there is no basis for an obviousness-type double patenting rejection.

The Examiner points out teachings from the prior art recited in the "Background of the Invention" section. This section does not provide any subject matter that explains how to

interpret the claims, and is not relevant to a rejection based on obviousness-type double patenting.

The Examiner points out methods described in column 3 (lines 54-60) and in column 4 (lines 63-66). One method is "preventing adverse effects associated with the use of a medical device in a patient wherein at least a portion of the device includes a nitric oxide adduct." The other method is "treating a damaged blood vessel surface or other injured tissue by locally administering a nitric oxide adduct to the site of the damaged blood vessel." However, these are not claims, and cannot be the basis for a rejection based on obviousness-type double patenting.

The Examiner states, "The selection of "nitric oxide adducts" of hemoglobin (e.g. (S) nitrosated/nitrated polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment). The Examiner is requested to clarify this statement. To what claim of the application does it refer, and to which claim of the cited patent does it refer? What meaning does "is anticipated or in the alternative obvious" have in the context of an obviousness-type double patenting rejection? The case referred to [*In re Schaumann*, 197 USPQ 5 (CCPA 1978)] has as its issue the question of whether the disclosure of a chemical genus may ever constitute a description of a specific compound falling within the ambit of the genus. The court concluded that the claimed species was obvious in view of the small recognizable class of compounds disclosed in the prior art reference, under 35 U.S.C. § 102(b). Applicants do not see the relevance of *In re Schaumann.*

The Examiner states that "[t]he prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount." Applicants cannot tell what prior art procedure is being referred to here, as no claim of US Patent No. 6,471,978 is referred to. Similarly, Applicants cannot tell what claim limitations of the present application are being referred to. In any case, the prior art procedure requires for all of Claims 1-65, administering or applying at least one nitric oxide adduct to a damaged vascular surface. Systemic administration of a nitric oxide adduct (S-NO-BSA) was ineffective (see Fig. 3) and is not within the meaning of Claims 1-65. For each of the rejected claims, nitrosated hemoglobin or nitrated hemoglobin or a nitrosyl-heme-containing donor of NO is required in an amount sufficient to achieve the objective stated in the preamble. This is not the same amount as used in the claims of US Patent No. 6,471,978. Further, for some of the rejected claims (16, 18, 21, 40

and 41), the composition administered in the method is not the same. Therefore, it cannot be true that "[t]he prior art procedure inherently meets claim limitations because the same protein is applied in the same way in the same amount."

## CONCLUSION

The Examiner is requested to consider the above remarks, and to withdraw the rejections. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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